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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,364	01/13/2004	Steven B. Landau	3506.1000-002	3343

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,364	LANDAU, STEVEN B.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *21-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/26/08, 1/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 1/24/2008. Claim(s) 1-62 are pending. Claim(s) 21-62 have been withdrawn. Claim(s) 1-20 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejections of the last Office Action are maintained for reasons of record and modified or repeated below for Applicant's convenience.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 83, 98, 113, 128, 142, 156 of copending Application No. 10/846,978. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims

are directed to a method of treating functional bowel disorders (irritable bowel syndrome) with a compound of formula I, whereas the referenced claims are directed to a method of treating a malady of the gastrointestinal tract with a compound of formula I, where the scope of formula I is identical. Accordingly, it is obvious to treat different forms of IBS, such as diarrhea-predominant and/or constipation-predominant IBS because the genus is taught to be treated with a compound of formula I. Examiner notes that this is a typical genus/species situation. Once a *prima facie* case of obviousness is established, the burden is shifted to the Applicant for objective evidence for nonobviousness. See MPEP 2144.08.

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-68 of copending Application No. 10/838,789; claims 63-130 of copending Application No. 10/841,318; claims 63-72 of copending Application No. 10/841,319; claims 63-130 of copending Application No. 10/866,593; claims 64-76 of copending Application No. 11/119,357; and claims 1-20 of copending Application No. 11/441,905. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims disclose a method of treating irritable bowel syndrome by administering a compound of formula I.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Claim amendments to Application No. 10/757,981 and 10/841,317 have rendered the obviousness double patenting rejection moot, therefore hereby withdrawn.

Claim amendments to Application No. 10/838,789; 10/841,318; 10/841,319 and 10/866,593 have rendered the provisional rejections under USC 101 moot, therefore hereby withdrawn. The following new obviousness double patenting rejections will now apply based on these applications.

Examiner acknowledges Applicant's desire to address the double patenting rejection based on claims 63-68 of Application No. 10/838,789 should this be the only remaining rejection on record.

Applicant's arguments directed to Application No. 10/846,978 are not persuasive because the referenced claims still recite a subject suffering from a malady of the gastrointestinal tract, which reads on the patient population of the instant invention.

Applicant's arguments directed to Application No. 11/119,357 and 11/441,905 are not persuasive because the patient population of the instant claims, subjects suffering from IBS, is also specified in the dependent claims of the Application No 11/119,357 and independent claims of Application No. 11/441,905.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim(s) 1-20 are rejected under 35 U.S.C. 103(a) as being obvious over Greenbaum et al. (*Digestive Diseases and Sciences*, vol. 32, no. 3, March 1987, 99.257-266, of record) in view of Ninomiya et al. (US Patent 4,695,568, of record).

The instant claims are directed to a method of treating irritable bowel syndrome (IBS) in a subject in need thereof comprising administering a compound of formula I.

Greenbaum et al. teach that anti-depressants, in general, and desipramine, specifically, can be used to treat irritable bowel syndrome. It is also disclosed that IBS can be diarrhea-predominant and/or constipation-predominant (abstract).

However, Greenbaum et al. fail to specifically disclose compounds of formula I.

Ninomiya et al. teach compounds of formula I can be used to treat depression (abstract). A preferred compound is disclosed to be 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine (claim 13). It is also specified that the Ar group of formula I may be a phenyl group, either unsubstituted or substituted with a halogen (claim 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have used a compound of formula I, specifically 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine, as disclosed by Ninomiya et al. for the treatment of irritable bowel syndrome as disclosed by Greenbaum et al.

A person of ordinary skill in the art would have been motivated to have used a compound of formula I, specifically 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine, as disclosed by Ninomiya et al. for the treatment of irritable bowel syndrome as disclosed by Greenbaum et al. because: (1) Greenbaum et al. teach that anti-depressants, in general, can be used to treat irritable bowel syndrome; (2) Ninomiya et al. teach that 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine can be used to treat depression; and (3) because of the reasonable expectation of similar efficacy in substituting one well-known anti-depressant for another. Therefore, the skilled artisan would have had a reasonable expectation of success in treating all forms of irritable bowel syndrome in a patient in need thereof comprising administering 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

Response to Arguments

Applicant argues that there is no reasonable expectation of success since Greenbaum discusses that reports of psychotropic agents (e.g. anxiolytics and antidepressants) in the treatment of IBS have been difficult to interpret for a number of reasons, such as inadequate definition of IBS, lack of placebo controls, and use of drug

combinations. Greenbaum further provides a summary of tricyclic antidepressants, reporting that some show usefulness, others do not, and still others show usefulness in some IBS studies and not others.

This is not persuasive because it is clear that Greenbaum shows actual data for the treatment of IBS by administration of at least one antidepressant, desipramine. The difficulty in treating IBS is not a result of the action of the antidepressants, but due to the difficulty in interpreting an adequate definition of IBS, lack of placebo controls, and use of drug combinations. Greenbaum shows in Tables 2 though 6, the data for desipramine, therefore at least one antidepressant has been shown to be useful in treating IBS. Moreover, nowhere in Greenbaum does it limit the usefulness of antidepressants in treating IBS to only desipramine or tricyclic antidepressants in general. Applicant is reminded that the standard for obviousness is not absolute, but a reasonable expectation of success.

Applicant argues that although Greenbaum teaches the tricyclic antidepressant, desipramine, to be useful in treating IBS, one of skill in the art would not expect that antidepressants generally will be useful in treating IBS, because of the diversity in structure and mechanism of action which exists among the various categories of antidepressants. Applicant also points out the differences in pharmacological profile between desipramine and MCI-225, as evidenced by Eguchi et al., in terms of antimuscarinic activity, 5-HT_3 receptor antagonist action, anticholinergic activity, and noradrenaline uptake inhibition.

This is not persuasive because Greenbaum does not attribute the mechanism of action in treating IBS to any particular mechanistic pathway. Greenbaum only surmises the potential possibility of central adrenergic, muscarinic, and serotonergic activities having any relevance in the treatment of IBS by antidepressants. Despite this, it is clear of the antidepressant role of desipramine in treating IBS as taught by Greenbaum (abstract; sentence bridging pg. 257-258; pg. 258, first sentence of second full paragraph; and pg. 264, first sentence of first full paragraph).

Claim(s) 1-10, 12, 14-20 are rejected under 35 U.S.C. 103(a) as being obvious over Bardsley et al. (WO 02/094249 A1, of record) in view of Sanger et al. (WO 94/01095, of record).

The instant claims are directed to a method of treating irritable bowel syndrome (IBS) in a subject in need thereof comprising administering a compound of formula I.

Bardsley et al. teach the use of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine for the treatment of pain (abstract).

However, Bardsley et al. fail to teach the nexus between pain and irritable bowel syndrome.

Sanger et al. teach that pain is a symptom of irritable bowel syndrome (pg. 1, line 10).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have used 4-(2-fluorophenyl)-6-

methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine as disclosed by Bardsley et al. for the treatment of irritable bowel syndrome as disclosed by Sanger et al.

A person of ordinary skill in the art would have been motivated to have used 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine as disclosed by Bardsley et al. for the treatment of irritable bowel syndrome as disclosed by Sanger et al. because: (1) Bardsley et al. teach the use of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine for the treatment of pain; (2) Sanger et al. teach that pain is a symptom of irritable bowel syndrome; and (3) since treating a symptom of a disease is considered treating the disease itself, treating pain is considered treating irritable bowel syndrome. Therefore, the skilled artisan would have had a reasonable expectation of success in treating irritable bowel syndrome by administering 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine.

Accordingly, it is obvious to treat different forms of IBS, such as diarrhea-predominant and/or constipation-predominant IBS because the genus is taught to be treated with 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine. Examiner notes that this is a typical genus/species situation. Once a *prima facie* case of obviousness is established, the burden is shifted to the Applicant for objective evidence for nonobviousness. See MPEP 2144.08.

Response to Arguments

Applicant argues that one of ordinary skill in the art would not expect that MCI-225 would be as effective in treating the visceral or nociceptive pain of IBS based on Bardsley's demonstration of treating inflammatory pain. In other words, the model of

inflammatory pain is not predictive of similar efficacy of MCI-225 in other types of pain, because the different types of pain (i.e., nociceptive, inflammatory, and neuropathic) are associated with differing underlying mechanisms, etiologies, and pathophysiologies and are treated with drugs specific for the type of pain. Applicant points out that Bardsley only exemplifies inflammatory pain only, whereas the visceral pain of IBS is not caused by inflammation.

This is not persuasive because while Bardsley's only example refers to treating inflammatory pain, Bardsley also teaches the use of MCI-225 for other types of pain (pg. 4). Specifically, it is taught that MCI-225 is useful for the treatment of nociceptive pain, which is the type of abdominal pain associated with IBS, as disclosed in Applicant's arguments on page 12.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

/SREENI PADMANABHAN/
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